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Title: Leukotriene (LT)C_4 aggravate bleomycin-induced pulmonary fibrosis in mice

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Body: Background: Synthesis of cysteinyl leukotrienes (cys-LTs) is thought to cause inflammatory disorders such as bronchial asthma and allergic rhinitis. Recent reports have suggested that LTC_4 is an important regulator of pulmonary fibrosis. This study examined the effect of LTC_4 in LTC_4 synthase-overexpressed transgenic (Tg) mice with bleomycin-induced pulmonary fibrosis. We also focused on the function of lung-derived fibroblasts in the Tg mice. Methods: Prior to administration of bleomycin, pranlukast hydrate, a cys-LT1 receptor antagonist, was intragastrically administered to Tg mice daily from the previous day of the administration. Bleomycin was administrated by intratracheal instillation. Concentrations of IL-4, -13, and TGF-β1 in BAL fluid were measured 14 days after the administration of bleomycin. And lung tissue was examined histopathologically. In addition, lung-derived fibroblasts from Tg and wild-type (WT) mice were cultured for 7 days, and LTC_4 secretion and cell viability were assessed by EIA and MTT assay, respectively. And the expression of TGF-β1 mRNA was measured by real time PCR. Results: The levels of IL-4, -13, and TGF-β1, and pulmonary fibrosis were greater in Tg than in WT mice. The reduction of LTC_4 function in Tg mice could be decreased both these cytokines and pulmonary fibrosis. Furthermore, continuous LTC_4 secretion from fibroblasts was higher in Tg than in WT mice, while reduction of LTC_4 by pranlukast in fibroblasts from Tg, but not in those from WT mice, decreased cell viability and expression of TGF-β1 mRNA. Conclusion: These findings first suggest that overexpression of LTC_4 using transgenic mice is responsible for the development of pulmonary fibrosis.